REMARKS

A check for the fee for a one month extension of time accompanies this response. Any fees that may be due in connection with filing this paper or with this application may be charged to Deposit Account No. 50-1213. If a Petition for extension of time is needed, this paper is to be considered such Petition.

Claims 10-18, 32-36, 38, 41 and 42 are presently pending in this application. Claims 10 and 32 are amended to more particularly point out and distinctly claim the subject matter. The amendment of claim 10 is to render its antecedents clear. Similarly, the amendment of claim 32 renders it clear that the step of "administering activation lowering therapy" is not the same as "a treatment for a disease or disorder."

No amendments have been made to obviate prior art and no new matter is added.

THE REJECTION OF CLAIMS 32-36, 38, 41, 42 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 32-36, 38, 41 and 42 remain rejected under 35 U.S.C. §112, first paragraph, as containing subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner continues to argue that the phrase "thereby preventing a disease" is allegedly not supported in the specification. The Examiner asserts that to prevent a disease, it must be totally eliminated and that evidence of this has not been shown on the record. This rejection is respectfully traversed.

The relevant law

The relevant law may be found in the prior Response.

Claim 32 and dependents

Claim 32 is directed to a method in which the level of cell activation in a subject is assessed as a diagnostic indicator. If the level is elevated, cell activation lowering therapy is administered. As shown in the application,

lowering cell activation levels can prevent a disease or disorder or improve treatment outcome. Hence, it is contemplated in this application that cell activation levels will be monitored as part of routine physical examinations and also prior to treatment where disease has been diagnosed. When part of a routine exam, the level can be used to assess risk; when used prior to undertaking a course of therapy for a disease or disorder, administration of cell activation lowering therapy can improve the outcome of the therapy for the disease or disorder especially in the advanced stages.

Analysis

Prefatory to the arguments presented below, it is noted that the Examiner appears to be confusing prevention with cure. Stating that the disease or disorder is totally eliminated implies that the disease or disorder was already present and the subject was cured. Prevention means that a subject may never manifest a disease or disorder.

It is shown in the instant application that the level of cell activation serves as a therapeutic intervention point (and also a diagnostic indicator) in diseased and in healthy individuals. If cell activation levels can be lowered, then a variety of diseases, such as stroke and other ischemic events, whose onset is exacerbated or mediated by cell activation can be prevented or treatment outcomes improved. To prevent a disease or disorder is to counteract the exacerbating or mediating forces in anticipation or advance of the disease or disorder occurring. In doing so, all or the most devastating consequences of such disease or disorder are averted. Preventing a stroke, for example, is not tantamount to curing a stroke. Preventing it means that all of the devastating consequences that would occur from a stroke are averted. Curing a stroke involves eliminating all of the consequences after they have occurred, such as aphasia and paralysis resulting from the stroke. Thus, prevention of the disease does not mean elimination of the disease and its root causes; prevention means to stave off a disease or disorder and the associated consequences.

As addressed in detail in the previous Response, applying the "Wands" factors to the instant claims demonstrates that in view of the scope of the claims and data and disclosure in the specification, it would not require undue experimentation to practice the claimed methods. Specifically, the observations presented in the application demonstrate that inappropriate levels of cell activation can exacerbate or mediate the onset of a disease or disorder. Thus, lowering cell activation levels can prevent the onset of a disease or disorder or reduce the severity thereof. Further, the results of experiments demonstrate prevention of disease.

Notwithstanding this, contrary to the Examiner's assertion, evidence has been presented on the record to show that administration of cell activation lowering therapy prevents disease. As stated on page 14 of the previous Response filed May 1, 2003, the results of the experiments presented in Example 8 of the specification demonstrate that in animals pretreated with serine protease, shock and mortality (the consequence of performing the SAO procedure) is completely prevented in SAO shock models.

As explained on the record, Example 8 of the specification (pages 136-145) provides results of experiments employing Splanchnic Arterial Occlusion (SAO) shock models effected either by arterial clamping or by bolus injection of pancreatic homogenate. As discussed in the specification, SAO shock is a form of shock that results from reduced blood flow to the splanchnic region. The main artery supplying the splanchnic region is the superior mesenteric artery, which arises directly from the aorta and feeds the pancreas, duodenum and mesentery of the small intestine. (Specification at page 83, lines 3-7). Reduced blood flow to the splanchnic region and mesenteric ischemia may result from "catastrophic to minimal illness, from arterial or venous occlusion to nonocclusive or low flow problems, from acute to recurrent to chronic process, from incidental end-stage circumstances to a primary disease or even an iatrogenic problem" (Williams, L., "Mesenteric Ischemia," *Surgical Clinics of*

North America, 68(2):331-353 (1988) (enclosed herewith)). Arterial occlusion, in particular, is associated with any number of diseases and conditions including, for example, emboli, cardiovascular diseases (including myocardial infarction, stroke, atherosclerosis, hypertension), aneurysms, trauma (including burns, surgery and sepsis), lupus, arthritis, diabetes mellitus and hereditary/genetic disorders (see, *e.g.*, Williams, Table 4).

Splanchnic arterial occlusion in rats is a well studied model of hypotension/ischemia-reperfusion injury (see, *e.g.*, Specification at page 82, lines 30-31; Haglind, E., *et al.*, "Graded Intestinal Vascular Obstruction: I. Description of an Experimental Shock Model in the Rat," *Circ. Shock*, 7:83-91 (1980) (enclosed herewith)). As stated above, this type of hypotension/ischemia-reperfusion injury is associated with many different diseases and disorder. The advantage of using the rat SAO shock model is that it is a well-established model with a more circumscribed region of tissue exposed to ischemia/reperfusion compared to the more global ischemia/reperfusion that can occur with many of the above listed disease and disorders. (Specification at page 83, lines 12). As seen in cases of global ischemia/reperfusion injury resulting from, for example, hemorrhagic shock, it was found that ischemia/reperfusion in the SAO shock model results in increased cell activation. (Specification at page 88, lines 10-12). The specification specifically states

> [t]he model of splanchnic arterial occlusion shock used in these experiments involves clamping the superior mesenteric artery as well as the celiac artery. The celiac artery supplies collateral flow to the superior splanchnic region (such as the pancreas) and ischemia to both arteries results in a much quicker and more uniformly lethal outcome than occlusion of the superior mesenteric artery alone. The third major supply vessel to the splanchnic region, the inferior mesenteric artery can also be clamped, but this results in large intestine and bowel necrosis which was unwanted in this study because of possible bacterial translocation. Clamping the superior mesenteric and celiac arteries insures almost complete

> ischemia to the pancreas while leaving the large intestines relatively well perfused. **This model of SAO shock has been well studied and is quite reproducible.** (Specification at page 82, lines 19-31, emphasis added)

In these experiments, animals pretreated with a serine protease such as futhan were compared with saline-pretreated control animals. The results show that performance of SAO shock protocols on saline-pretreated control animals results in uniform hypotension (shock) and death. In animals pretreated with serine protease prior to performance of the SAO procedure, shock and mortality is completely prevented, *i.e.*, all of the devastating consequences that occur as a result of performing the SAO procedure are averted by pre-treatment with serine protease (see, *e.g.*, page 32, line 10-17; page 137, line 25 to page 138, line 2; and page 144, line 20). As indicated above and in the specification, shock is marked by **uniform** hypotension. The transient decrease in blood pressure or brief hypotension that was reported in animals pretreated with serine protease (see, *e.g.*, page 32, lines 15-16; page 137, line 25 to page 138, line 2; and page 144, line 20) is not tantamount to shock. As specifically stated at page 32, line 15, futhan pretreated "animals did not go into shock." Thus, prevention of shock was complete. Example 8 provides ample evidence to support the prevention of disease by administration of activation lowering therapy as required by the claims. Therefore, the application shows that a disease can be prevented (*i.e.*, never develop).

THE REJECTION OF CLAIMS 10-18, 32-36, 38, 41 and 42 UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 10-18, 32-36, 38, 41 and 42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating hemorrhagic shock by assessing free radical production using phenol red and then, if levels are elevated using futhan, is allegedly not enabling for any and all activation lowering therapies and any and all diseases or conditions and any and all methods of assessing cellular activation. The Examiner reasons that the art

of biotechnology is a highly unpredictable art and it would be an undue burden for one of skill in the art to test any and all activation lowering therapies and any and all diseases or conditions and any and all methods of assessing cellular activation to see if they could perform the claimed processes.

This rejection is respectfully traversed. As discussed below, the therapeutic target and diagnostic indicator is cell activation. Numerous methods and ways to lower cell activation are provided in the specification; these range from particular drugs, such as futhan, to lifestyle changes. Cell activation is a phenomenon that is known to those of skill in the art as are factors that lead to its elevation and some methods for its decrease. Prior to the instant application, however, cell activation has not been identified as a diagnostic or prognostic of disease or treatment outcome nor as a point of therapeutic intervention. Having identified it as such in the instant application, then each step in the method, from testing the levels of cell activation to lowering levels, are known to those of skill in the art. Further, the specification provides detailed guidance for cell activation lowering protocols. Again, most of these protocols, changing diet, reducing stress are not unpredictable heretofore unknown regimens. Anything that lowers cell activation is contemplated by the specification.

The specification provides numerous examples of different cell activation therapies and methods for identifying cell activation therapies. Further, the specification provides a specific definition of cell activation and, based on this definition, provides numerous methods for assessing it. Also, the specification provides detailed disclosure of how cell activation therapy works and under what circumstances it may be used. As presented in detail below, although the choice of therapy may be influenced by various factors including general health of the subject and/or symptoms of a disease or disorder, the specific disease or disorder from which a subject may be suffering is of no consequence in the method. Cell activation is the target of the therapy, not any particular disease or disorder. The consequence of lowering cell activation (if levels are

determined to be high) is the same for any disease or disorder; *i.e.*, outcome of treatment (for the disease or disorder) is improved and risks associated with treatment (for the disease or disorder) are reduced.

The relevant law

The relevant law may be found in the prior Response.

Analysis

As stated in the previous Response, there is no requirement for a specific example of everything within the scope of a broad claim. Applicant is entitled to claims that are commensurate in scope not only with what Applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the Applicant has disclosed. The inquiry with respect to scope of enablement, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation.

As detailed in our previous Response with respect to the enablement rejection addressed above, the specification provides detailed disclosure regarding activation lowering therapy and assays for assessing cellular activation. Indications for use of cell activation assessment and therapy are also clearly outlined in the specification and our previous Response. (See discussion of Forman factors on pages 4-16 or previous Response). Based on the disclosure in the specification, it would not require undue experimentation to use the claimed methods. The relevant arguments are provided again below in revised form.

As shown in the application the activation status of neutrophils and other inflammatory cells is an important diagnostic indicator. Cell activation levels are of central importance not only in disease states, such as ischemia, infection, trauma, inflammatory diseases, but also in 'healthy' individuals. It is shown in the application that cellular activation can be used generally as a diagnostic indicator and an indicator of therapeutic outcome in individuals with a disease or

disorder or in apparently healthy individuals. As shown in the application it is a therapeutic target for preventing development of diseases and also improving outcomes of treatments for disease. The instant claims are not directed to treatment of particular diseases, but to identifying the level of cell activation, and then if necessary lowering it prior to or concurrent with treatment for a particular disease. The cell activation lowering therapy **is not** the treatment for the disease.

Indications for use

As shown in the application, cell activation levels are significant generally, whether in good or poor health. Cell activation assays and cell activation lowering therapy can be used, respectively, as diagnostic and therapeutic procedures in a wide variety of clinical settings. It is envisioned in the application, that measurement of cell activation levels will become a routine part of a physical exam and also prior to treatment for a disease or trauma. The level of cell activation is prognostic of the risk of developing diseases and also is an indicator of the outcome of a treatment. A trauma patient with high cell activation levels, will have a poorer surgical outcome. Knowledge of the cell activation level can guide therapeutic decisions. It is these findings that are encompassed by the pending claims. The application describes them in great detail (see, *e.g.*, section C of the specification starting at page 25 and schematically in Figure 2). For example, cell activation measurement and therapy can be used in healthy individuals as follows:

> Identification of healthy individuals with elevated levels of activated cells, permits early identification of at-risk individuals and permits early intervention, in chronic and also in acute diseases. As shown in Figure 2, in a seemingly healthy patient activation levels are measured. If low, then no treatment or changes in lifestyle are recommended. If the levels are elevated (above the 50th percentile, more likely above the 20th percentile, or one standard deviation above the mean or more), then tests to determine the presence of subclinical infection or other cell activating condition are performed. If those tests are negative, then lifestyle and diet

> should be examined, and if, necessary, modified. If diet is good, and lifestyle is generally good and stress-free, then activating lowering therapy can be instituted. (Specification at bottom of page 24.)

Cell activation measurement and therapy also can be important prior to surgery.

> Testing cell activation levels pre-surgery, particularly elective surgery, can be used to assess the likelihood of complications from surgery and organ transplant rejection. If high levels of cell activation that are not the result of infection are found, then surgery should be postponed and activation lowering therapy considered. Similarly, in unstable angina, the levels of cell activation are indicative of the risk of a cardiovascular event. Thus, if levels are high, activation lowering therapy and/or more aggressive treatment should be pursued. In trauma situations, the level of cell activation can aid in selecting treatment protocol and timing thereof. High levels of activation are associated with ARDS and MOF in the emergency room. Activation lowering therapy should reduce the risk thereof. (Specification at top of page 25.)

Cell activation assessment and therapy also is important prior to or in conjunction with treatment for a disease or disorder other than surgery. For example, the specification states that

> inappropriate or excessive activation leads to or participates or intensifies many diseases, including, but not limited to: arthritis, atherosclerosis, acute cardiovascular incidents, Alzheimer's Disease, hypertension, diabetes, venous insufficiency, autoimmune disease and others. Cell activation is a major contributor to rejections processes in organ transplants, and to predisposition to poor outcomes in trauma and high risk surgeries. (specification at bottom of page 16 to top of page 17.)

The specification specifically states that cell activation is relevant in the diagnosis and treatment of chronic disease such as diabetes, atherogenesis, and venous insufficiency. Further, FIGURE 1 provides a summary of the relation of cell activation to disease showing that cardiovascular cell activation plays a central role in cardiovascular diseases and immune response and that it responds to lifestyle factors, as well as trauma, ischemia, infection; initiates or

potentiates atherosclerosis; causes poor outcome in trauma, shock, MI; and participates in a disease positive feedback loop.

Thus, cell activation therapy is of significant importance in both healthy and disease states because inappropriate levels of cell activation can generally put a subject at risk of developing disease, exacerbate an existing disease, and/or predispose a subject to poor outcomes of treatment for a disease. Although the choice of therapy may be influenced by various factors including general health of the subject and/or symptoms of a disease or disorder, the specific disease or disorder from which a subject may be suffering is of no consequence in the claimed method. Cell activation is the target of the therapy, not any particular disease or disorder. The consequence of lowering cell activation (if levels are determined to be high) is the same for any disease or disorder; *i.e.*, outcome of treatment (for the disease or disorder) is improved and risks associated with treatment (for the disease or disorder) are reduced.

Methods for assessing cell activation

Cell activation is defined in the specification as "changes in and interactions among circulating white blood cells, including leukocytes, cells lining blood vessels, including endothelial cells, and platelets. These changes are evidenced by increased "stickiness" of cells, changes in shapes of cells, free radical production and release of inflammatory mediators and enzymes. Activated cells project large pseudopods, and express adhesion molecules on their surfaces." (Specification at page 16, lines 18-24). The specification provides many detailed assays for assessing cell activation levels based on the characteristics of cell activation described above. Further, any method known to measure one or more of the aforementioned characteristics of cell activation can be used to assess cellular activation. For example, at page 12, the specification teaches cell activation can be "assessed [by] superoxide production, such as defined by the nitroblue tetrazolium test and lucigenin-enhanced chemiluminescence, and/or actin polymerization, such as defined by

the pseudopod formation test." Starting at page 26, the specification describes a variety of exemplary cell activation assessment assays:

> The tests, discussed and exemplified below in more detail below and include tests that assess indicators of activation, such as changes in shape and free radical production. For example cell morphological changes may be quantified with direct microscopic examination, with or without fluorescent staining of F-Actin filaments present in pseudopods, or with fluorescence activated cell sorting techniques. Superoxide anion production can be detected and quantified using chemiluminescence generating reagents, such as luminol, isoluminal and lucigenin, that quantitatively react therewith. Free radicals can be assessed by NBT (nitroblue tetrazolium). Adhesion can be assessed by various immunassays that detect surface adhesion molecules, such as CD11, CD18 and L-selectin and others. Other indicators of activation include expression of certain factors, such as interleukin and TNF-α, which can be measured by known immunoassays.
>
> Activation can also be assessed by sampling plasma and determing whether it activates cells, such as endothelial cell cultures. Plasma can be tested for clastogenic activity by standard methods. Although there is a high correlation between the different cell activation assay measures, it is likely that there will be different combinations of indicators which are most informative in any situation. For example, plasma activator levels might be high but circulating activated neutrophil counts low due to sequestration of the activated cells in the microcirculation. Also, genetic, age, and environmental differences between patients will complicate the interpretation of the assays. Clinical tests are in preparation to relate statistically cell activation measures to disease outcomes, to find the formulas which are invariant to patient differences, and to establish the best predictive procedures and activation lowering therapies in different situations. The measurement of cell activation and circulating plasma factors also serves as an effective tool to evaluate the effectiveness of new interventions prior to execution of full-scale clinical trials. Drug candidates thereby may be rejected, or patient populations enriched for more favorable response to the candidate drug.

Detailed cell activation protocols are described in Section E (page 35 *et seq.*) of the specification.

> Rates of free radical production in whole blood can be measured using phenol red (Pick et al. (1980) J. Immunol. Methods 38:161-170) or other dye forming reagents (U.S. Patent No. 5,518,891). Intracellular

radical production may be measured with nitroblue tetrazolium (NBT) reduction or chemiluminescence (Cheung et al. (1984) Aust. J. Expt. Biol. Med. Sci. 62:403) assays. Radical production in whole blood or plasma may be measured electrochemically, and mRNA expression of specific genes can be quantitated, for example, using Northern blots or DNA microarrays.

Expression of adhesion molecules such as CD11b, CD18, and of L-Selectin can be quantitated via flow cytometry, while cytokines and chemokines, such as interleukins and TNF-a can be quantitated with immunoassays.

Cell morphological changes may be quantified with direct microscopic examination, with or without fluorescent staining of F-Actin filaments present in pseudopods, or with fluorescence activated cell sorting techniques.

Blood plasma is known to carry cell activation factors in response to specific events. Plasma from I/R episodes including MI (Chang et al. (1992) Biorheology 29:549-561) and hemorrhagic shock (Elgebaly et al. (1992) J. of Thoracic and Cardiovascular Surgery 103(5):952-959; Paterson et al. (1993) Am. Vasc. Surg. 7(1):68-75; Barroso-Aranda et al. (1995) J. Cardiov Pharmacology 25(Suppl 2):S23-S29) activates neutrophils, as does plasma from smokers' blood (Pitzer et al. (1996) Biorheology 33(1):45-58). Patient blood samples can be applied to standard donor cells and the response of the donor cells used as a measure of the potency of the circulating activating factors in the patient blood.

The specification provides working examples (see, *e.g.*, EXAMPLES 1, 2 and 6), including description of an electrode method for measuring hydrogen peroxide, which is correlated with cell activation levels.

Activation lowering therapy

The Examiner asserts that the specification is not enabled for any and all activation lowering therapies. It is respectfully submitted that cell activation is the therapeutic target. Thus, anything that lowers cell activation is contemplated by the specification; the specification provides a variety of methods for lowering cell activation. Selection of a method will be dependent upon circumstance. For example, a change in lifestyle or diet is not likely to

benefit a trauma patient; for such patient a more immediate treatment, such as treatment with a protease inhibitor, is warranted.

As discussed above under **Indication for use**, the specification provides a detailed framework for how a particular therapy may be chosen. For example, in the case of a seemingly healthy patient, if the levels are elevated (above the 50th percentile, more likely above the 20th percentile, or one standard deviation above the mean or more of a healthy control group), then tests to determine the presence of subclinical infection or other cell activating condition are performed. If those tests are negative, then lifestyle and diet should be examined, and if, necessary, modified. If diet and lifestyle are generally not stimulating cell activation, then more invasive therapy such as administration of specific cell activation lowering pharmaceuticals or procedures can be instituted.

Although it is clear that the choice of cell activation lowering therapy will likely depend on the individual circumstance as discussed above, anything that lowers cell activation can be used as a diagnostic intervention such as to prevent a disease or disorder, improve treatment outcome for a particular disease or disorder, or reduce the risk of a treatment for a particular disease or disorder. Selection of treatment is a function of the patient and circumstances.

Further, the specification lists in detail many of the different types of therapies from which to choose. As defined on page 19:

> activation lowering therapy (A.L.T.) refers to any means in which the level of activated cells is lowered. Such means include lifestyle and dietary changes, drug therapy, such as aspirin, pentoxifylline, Daflon 500 (a flavonoid), anti-inflammatories, inderal, heparin, coumadin, Futhan and other protease inhibitors.

These cell activation lowering protocols and others are described throughout the specification (see, *e.g.*, page 13 and page 25, lines 15-20). For example, it is stated that lifestyle changes include, for example, stress management, exercise and diet. Drug therapy includes administration of known pharmaceuticals or drugs such as those listed above as well as other heart medications. Dialysis

and other such procedures are also included. As indicated, protease inhibitors, such as serine proteases, including futhan, can be administered.

Further, the specification provides detailed methods for identifying compounds that lower cell activation. For example, the specification provides a pancreatic homogenate that can be used as a screening tool for identifying agents that inhibit cell activation, including protease inhibitors (see, *e.g.*, pages 29-33; section H, top of page 46).

Rebuttal the Examiner's Specific Statement

The Examiner states "Applicant has only shown treating hemorrhagic shock by assessing for free radical production using phenol red and then if levels are elevated, using futhan." It should be clear from the forgoing discussion that this assertion is incorrect and is based on a misunderstanding of the claimed subject matter. To show the flaws in the Examiners specific statement, the specific steps of each independent claim are discussed in detail.

Claim 10 is directed to a method of improving treatment outcome or reducing risk of treatment by:

> assessing treatment options for a disease or condition by measuring cell activation levels in a subject; and, if elevated, administering activation lowering therapy prior to commencing further treatment for the disease or condition, thereby improving treatment outcome or reducing risk of treatment.

It is respectfully submitted that the method is not directed to "treating hemorrhagic shock" or any particular disease or disorder. The method is based on lowering cell activation levels. In the method of claim 10, **options** for treating a disease or disorder (*e.g.*, options for treating hemorrhagic shock) are assessed by first measuring cell activation levels. As discussed above, the specification provides numerous assays, not just the phenol red assay, based on specific characteristics of cell activation described in the specification. Further, any method known to measure one or more of the aforementioned characteristics of cell activation can be used to assess cellular activation. As

described in the specification, knowing the level of cell activation is useful for guiding therapeutic decisions such as postponing surgery, choosing from more or less aggressive therapies for a disease or disorder and choosing whether or not to administer cell activation lowering therapy prior to commencing any treatment for the disease or disorder. Specifically,

> [t]esting cell activation levels pre-surgery, particularly elective surgery, can be used to assess the likelyhood of complications from surgery and organ transplant rejection. If high levels of cell activation that are not the result of infection are found, then surgery should be postponed and activation lowering therapy considered. Similarly, in unstable angina, the levels of cell activation are indicative of the risk of a cardiovascular event. Thus, if levels are high, activation lowering therapy and/or more aggressive treatment should be pursued. In trauma situations, the level of cell activation can aid in selecting treatment protocol and timing thereof. High levels of activation are associated with ARDS and MOF in the emergency room. Activation lowering therapy should reduce the risk thereof. (Specification at top of page 25.)

The method requires treating inappropriate cell activation level if levels are determined to be high prior to commencing any treatment for the disease (*e.g.*, hemorrhagic shock). Thus, following the steps of the method, cell activation levels would be assessed and, if determined to be high, cell activation lowering therapy would be administered (this would entail treatment, such as futhan, to lower the elevated cell activation level). Once activation levels are lowered, a treatment for the disease or disorder (whatever that treatment might be) may be commenced. In lowering cell activation levels by administering cell activation lowering therapy prior to treating the hemorrhagic shock, the outcome of treatment for the shock will be improved or the risk associated with treatment for the shock will be reduced.

Because cell activation is a condition of the immune system, it is clear that an inappropriate level has the potential of contributing to or exacerbating any disease or disorder and that lowering such levels will increase the likelihood that treatment of any existing disease or disorder will be improved. It has also

shown that lowering cell activation in a seemingly health individual can prevent a disease or disorder. This is discussed in detail above and a specific example of how the method of claim 32 may be employed is given below. Claim 32 is directed to a method including the steps of

> assessing cell activation in a subject; and, if elevated, administering activation lowering therapy, thereby preventing a disease or disorder or reducing the risk of a poor outcome of a treatment of a disease or disorder.

As it is envisioned in the application, measurement of cell activation levels will become a routine part of a physical exam. Thus, an otherwise healthy individual may have his cell activation level assessed. Identification of healthy individuals with elevated levels of activated cells, permits early identification of at-risk individuals and permits early intervention, in chronic and also in acute diseases. If activation levels are normal, then no activation lowering therapy is recommended. If the levels are elevated (above the 50th percentile, more likely above the 20th percentile, or one standard deviation above the mean or more), then activating lowering therapy can be instituted. Therapy may include lifestyle and diet changes or more invasive therapy, such as drug therapy. By lowering cell activation levels, it is possible to prevent the onset of a disease or disorder or, if the elevated levels were found to be linked to a previously undetected disease or disorder, it possible to reduce the risk of a poor outcome of any subsequent treatment for the disease or disorder.

Applicant has shown that inappropriate or excessive cell activation leads to or participates in or intensifies disease states generally. Thus, it is advantageous to assess cell activation whether a subject is in good or poor health. The specification is enabling for a wide variety of methods of assessing cell activation, not just the phenol red assay. If levels are determined to be high, lowering cell activation is, in general beneficial. As addressed in detail above, the therapy and the specific benefit derived from the therapy will depend on the circumstance. If the patient is suffering from a disease or disorder,

administering activation lowering therapy alleviates a condition (inappropriate cell activation) that would otherwise contribute to or exacerbate the disease, increasing the likelihood of a poor outcome of treatment for the disease.

Thus, the Examiner's statement that Applicant shows "treating hemorrhagic shock by assessing for free radical production using phenol red and then if levels are elevated, using futhan" is incorrect.

Conclusion

Since cell activation, as defined in the specification, is a well documented and normal physiological response of the immune system that is essential for survival and since inappropriate or excessive levels of cell activation have been found to be of significant importance generally, whether in good or poor health, it follows that assessment of cell activation levels and treatment of inappropriate levels is relevant whether a subject presents symptoms of a disease or not. And, although it is clear that the choice of cell activation lowering therapy will likely depend on the individual circumstance as discussed above, the actual disease or disorder (if one should be present) is of little consequence. It is clear that cell activation therapy is relevant anytime inappropriate levels of cell activation are found and that inappropriate levels may appear in conjunction with or as a result of any disease or disorder that invokes an immune response or in the absence of any apparent disease or disorder. The specification provides ample guidance for identifying and choosing a particular therapy. The specification also provides ample guidance for identifying and choosing a method for assessing cellular activation. It is clear that any method of assessing cell activation or combination of methods may be used. Thus, the methods as claimed are fully enabled by the specification.

THE REJECTION OF CLAIMS 10-18, 32-36, 38, 41 and 42 UNDER 35 U.S.C. 112, SECOND PARAGRAPH

Claims 10-18, 32-36, 38, 41 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and

distinctly claim the subject matter which Applicant regards as the invention. Various bases for this rejection are set forth and each is discussed in turn below. Reconsideration of the grounds for rejection is respectfully requested in view of the following remarks.

Relevant Law

Definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of prior art, and (3) the interpretation claims would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. Claims need only "reasonably apprise those skilled in the art" of their scope and be "as precise as the subject permits." Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 94 (Fed. Cir. 1986), cert. den., 480 U.S. 947 (1987). The Court in Orthokinetics, Inc v. Safety Travel Chairs, Inc., 1 USPQ2d 1081 (Fed. Cir. 1986) held that a claim limitation requiring that a pediatric wheelchair part be "so dimensioned as to be insertable through the space between the doorframe of an automobile and one of the seats" is definite. The Court stated:

> The phrase 'so dimensioned' is as accurate as the subject matter permits, automobiles being of various sizes. As long as those of ordinary skill in the art realized that the dimensions could be easily obtained, § 112, 2d ¶ requires nothing more. The patent law does not require that all possible lengths corresponding to the spaces in hundreds of different automobiles be listed in the patent, let alone that they be listed in the claims.

1 USPQ2d at 1088.

When one skilled in the art would understand all of the language in the claims when read in light of the specification, a claim is not indefinite.

Applicant is unaware of any requirement that terms be defined in the claims when one of skill in the art can readily determine the meaning of the term based on the description and definitions provided in the specification. In this respect, Applicant is entitled to be its own lexicographer [see, *e.g.*, MPEP

2111.01 "Applicant may be his or her own lexicographer as long as the meaning assigned to the term is not repugnant to the term's well known usage and utilize terms within the claims that are clear from a reading of the specification]. In re Hill, 73 USPQ 482 (CCPA 1947)". When Applicant has provided definitions in the specification, the claims are interpreted in light of such definition.

35 U.S.C. §112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. The claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. Shatterproof Glass Corp. v. Libby-Owens Ford Col, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir), cert dismissed, 106 S. Ct. 340 (1985).

The amount of detail required to be included in the claims depends on the particular invention and the prior art and is not to be viewed in the abstract, but in conjunction with whether the specification is in compliance with the first paragraph of 35 U.S.C. §112. If the claims, read in light of the specification, reasonably apprise those skilled in the art of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more:

> [i]t is not necessary that a claim recite each and every element needed for the practical utilization of the claimed subject matter (Bendix Corp. v. United States, 600 F.2d 1364, 1369, 220 Ct. Cl. 507,514, 204 USPQ 617, 621 (1979); See, also, Carl Zeiss Stiftung v. Renishaw plc, 20 USPQ2d 1094, 1101).

Analysis

1) It is allegedly unclear how the method can perform a prophylaxis, diagnosis, and treatment all at the same time because Applicant has allegedly argued, contradictory to the claimed methods, that the method is a way of diagnosis and that it does not treat a condition or disease. It is alleged that

Applicant has argued that the references only teach treating the condition or disease and that the claims are drawn to a diagnosis.

Claim 32 has been amended to remove the portion of the preamble that recites "prophylaxis, diagnosis and treatment." This does not change the scope of the claimed subject matter since the preamble is not limiting. The steps of the method are the limiting part of the claim. Here, the method includes the steps of assessing cell activation and, if elevated, administering activation lowering therapy, thereby preventing a disease or disorder or reducing the risk of a poor outcome of a treatment of a disease or disorder.

As amended, the language of claims 32 is sufficiently clear that one skilled in the art would understand the metes and bounds of the claim when read in light of the specification.

It is respectfully submitted that the Examiner has misunderstood Applicant's arguments. Applicant argued that the specific **step** of the method, administering activation lowering therapy, is not treatment for a particular disease (see, *e.g.*, previous Response at bottom of page 20). The step of administering activation lowering therapy is to lower cell activation. Applicant further argued that none of the references teaches or suggests this step of the claimed method, *i.e.*, administering activation lowering therapy (such as futhan) to lower cell activation levels. In all references in which futhan is administered, it is administered as the treatment for a disease, not as cell activation lowering therapy (see, *e.g.*, previous Response at middle of page 25). As detailed in the specification, activation lowering therapy can be administered either prior to (or simultaneous with) a treatment for a particular disease or disorder. As detailed in the specification and discussed on the record, such therapy (*i.e.*, cell activation lowering therapy) can improve the outcome of a treatment for a disease or disorder, reduce the risk associated with a treatment for a particular disease or disorder (claim 10), or can be prophylactic where there is no evidence of disease or can reduce the risks of a poor outcome of treatment of a particular

disease or disorder (claim 32). Thus, as stated in our previous Response, the instant claims are directed to methods in which levels of cell activation are assessed, and if elevated, are reduced by cell activation lowering therapy. The therapy is not a treatment for the underlying disease, but to reduce levels of cell activation (see, e.g, page 37, end of first full paragraph).

2) It is allegedly unclear what is meant by the phrase "cell activation."

It is respectfully submitted that "cell activation" is thoroughly described in the application and is well known to those of skill in the art. As defined in the application on page 16, lines 19-25, and submitted on page 20 of the previous Response, cell activation refers to changes in and an upward shift in the level of interactions among circulating white blood cells, including leukocytes, cells lining blood vessels, including endothelial cells, and platelets. These changes are evidenced by increased "stickiness" of cells, changes in shapes of cells, free radical production, release of inflammatory mediators and enzymes, pseudopod formation, and expression of adhesion molecules. Further, as stated in the application (see pages 3-11), at the time of the effective filing date of this application and before, the skilled artisan knew that cells in microcirculation can be encountered in a relatively quiescent state and in various stages of activation. It was also known that cell activation is a normal physiological response that is essential for survival from infection and is brought about by certain cellular activating factors. It was also known that inappropriate activation is implicated in the pathology of many disease processes. In particular, there was evidence that cardiovascular complications, such as myocardial infarction, venous ulceration and ischaemia/reperfusion injury may be associated with an activation of cells in circulation such as neutrophils and other inflammatory cells. Further, there was a large body of literature, incorporated in the instant specification by reference (see, *e.g.*, pages 5-10), that was directed to the identification of factors responsible for cellular activation. Hence, it is

clear to the skilled artisan what is meant by "cell activation" as used in the claims and defined in the specification.

3) It is allegedly unclear what is meant by the phrase "if elevated."

It is respectfully submitted that specification thoroughly describes and provides examples of what is meant by the phrase "if elevated." For example, on page 25, it is stated that cell activation is considered elevated when

> [it] is above the normal range, which can be established by sampling "healthy" people and determining the mean. In particular, individuals with activated cells in the upper 20% of levels or one standard deviation above the mean are considered candidates for activation lowering therapy.

Thus, the metes and bounds of the claims are sufficiently clear when read in light of the specification.

4) It is allegedly unclear what is meant by the phrase "administering activation lowering therapy." As discussed in detail above and defined on page 19:

> activation lowering therapy (A.L.T.) refers to any means in which the level of activated cells is lowered. Such means include lifestyle and dietary changes, drug therapy, such as aspirin, pentoxifylline, Daflon 500 (a flavonoid), anti-inflammatories, inderal, heparin, coumadin, Futhan and other protease inhibitors.

Thus, administration of therapy can be a lifestyle regimen including, for example, stress management, exercise and/or diet regimen. Administration of therapy can also mean drug therapy including, for example, administration of known pharmaceuticals or drugs such as those listed above and throughout the specification. As indicated, protease inhibitors, such as serine proteases, including futhan, can be administered. Administration of therapy can also mean dialysis and other such procedures which are known to lower cell activation as described in the specification.

5) It is allegedly unclear what is meant by the phrase "preventing a disease or disorder." The Examiner reiterates his contention that for the disease to be prevented the disease would have to be totally eliminated.

As discussed in detail above, to prevent a disease or disorder is, not to eliminate it, but to counteract the exacerbating or mediating forces in anticipation or advance of the disease or disorder occurring. In doing so, all the devastating consequences of such disease or disorder are averted. Contrary to the Examiner's assertion, prevention is taught in the specification (see detailed discussion above).

THE REJECTION OF CLAIMS 10-18, 32-36, 38, 41 and 42 UNDER 35 U.S.C. §103

Claims 10-18, 32-36, 38, 41 and 42 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Okada *et al.*, (1991) *Journal of International Medical Research 19*:234-236 (Okada 1), Okada *et al.*, (1991) *Journal of International Medical Research 19*:348-350 (Okada 2), Yanamoto *et al.*, or Yonekura *et al.*, in view of Gibboni *et al.*, Pick *et al.*, Babcock *et al.*, and Brunck *et al.*

In response to Applicant's arguments filed May 1, 2003, in which Applicant asserted that none of the references singly or in combination taught or suggested the elements of assessing cell activation and administering cell activation lowering therapy, the Examiner rebuts without providing any support from the cited references or otherwise, that "as explained on the record, a doctor would want to check [cell activation] levels before administering futhan since otherwise futhan would not be needed." The Examiner asserts that the first step of claim 32 is to assess cell activation which will tell the doctor if the patient needs the medication. The Examiner alleges that this is a "normal thing for a doctor to do."

Prefatory to the rebuttal presented below, it is respectfully submitted that there is no explanation of record to support the Examiner's assertion. Further,

the Examiner has never before made this exact assertion. The Examiner's similar assertions and our rebuttal to each is set out in the previous Response on pages 34-38.

There is no teaching or suggestion in any cited reference that supports the Examiner's reasoning that "a doctor would want to check [cell activation] levels before administering futhan since otherwise futhan would not be needed." There is no art of record that demonstrates that doctors check cell activation levels as a screening tool or diagnostic or prognostic tool, nor that a doctor would then administer cell activation lowering therapy.

Detailed analysis of differences between the claims and the combination of teachings of the cited references is provided on pages 19-29 of the previous Response. As argued in our previous Response, none of the cited art teaches or suggests that futhan lowers cell activation. The references directed to the use of futhan teach administration of futhan only with respect to complement activation associated with insulin-dependent diabetes mellitus, cerebral vasospasm after aneurysmal subarachnoid hemorrhage, disseminated intravascular coagulation and pancreatitis resulting from digestive enzymes activated by trypsin. There is no mention of cell activation in these references. Thus, these references cannot suggest a method (Claim 10 and dependents) that includes the steps of:

(1) assessing treatment options for a disease or condition by measuring cell activation levels in a subject with the disease or condition; and,

(2) if cell activation levels are elevated, administering activation lowering therapy prior to commencing treatment for the disease or condition, thereby improving treatment outcome or reducing risk of treatment.

The combination does not suggest a method (claim 32 and dependents) in which the level of cell activation of a subject is assessed as a diagnostic indicator. If the level is elevated, cell activation lowering therapy is

administered. In none of the references, singly or in any combination thereof, are these two steps taught or suggested.

> To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher *W.L. Gore & Associates, Inc. v. Garlock Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 312-13 (Fed. Cir. 1983).

It is respectfully submitted that it is inappropriate for the Examiner to pick references that teach administration of futhan and conclude that futhan was used to lower cell activation when none of the references states that futhan was used for this purpose. Only the instant application teaches that it is desirable to lower cell activation and that compounds like futhan can be used for this purpose. It is, therefore, also inappropriate to conclude that it would be obvious for a doctor to check cell activation levels before administering futhan. Only the instant application teaches that cell activation levels can be used as a therapeutic target. None of the references teaches or suggests this. If the Examiner is basing his assertion on the cited references, then he has improperly relied on hindsight in setting forth the rejection.

If the Examiner is taking judicial notice by asserting that "... a doctor would want to check [cell activation] levels before administering futhan since otherwise the futhan would not be needed," the Examiner is reminded that MPEP 2144.03 states:

> The Examiner may take official notice of facts outside of the record which are capable of instant and unquestionable demonstration as being "well-known" in the art. In re Ahlert, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). . . ..

The conclusion that a doctor would want to check cell activation levels then administer cell activation lowering therapy, such as administration of futhan to lower cell activation, before administering treatment for a disease or disorder or to prevent or reduce the severity of a disease or disorder is not

"capable of instant and unquestionable demonstration as being 'well-known' in the art." The Examiner has not cited any art that demonstrates that futhan lowers cell activation or that cell activation levels should be lowered at all or that a doctor would check the cell activation levels, and administer cell activation lowering therapy.

MPEP 2144.03 continues:

> If justified, the examiner should not be obliged to spend time to produce documentary proof. If the knowledge is of such notorious character that official notice can be taken, it is sufficient so to state. In re Malcolm, 129 F.2d 529, 54 USPQ 235 (CCPA 1942). If the applicant traverses such an assertion the examiner should cite a reference in support of his or her position.

In this instance, there is no evidence that one of ordinary skill in the art would be motivated to assess cell activation levels. Contrary to the Examiner's assertion, there is no evidence of record to establish that this is "a normal thing for a doctor to do." Further, there is no evidence that one of ordinary skill in the art would know that futhan can be used to reduce cell activation levels. This area of technology is of an esoteric nature, since it is to be used by those in the medical profession. For esoteric technology, MPEP 2144.03 states:

> ("[A]ssertions of technical facts in areas of esoteric technology must always be supported by citation of some reference work" and "allegations concerning specific 'knowledge' of the prior art, which might be peculiar to a particular art should also be supported." Furthermore the applicant must be given the opportunity to challenge the correctness of such assertions and allegations. "**The facts so noticed serve to 'fill the gaps' which might exist in the evidentiary showing" and should not comprise the principle evidence upon which a rejection is based.**). See also In re Barr, 444 F.2d 588, 170 USPQ 330 (CCPA 1971) (scientific journal references were not used as a basis for taking judicial notice that controverted phrases were art-recognized because the court was not sure that the meaning of the term at issue was indisputable among reasonable men); and In re Eynde, 480 F.2d 1364, 1370, 178 USPQ 470, 474 (CCPA 1973) ("The facts constituting the state of the art are normally subject to the possibility of rational disagreement among reasonable men and are not amenable to the taking of [judicial] notice.").

In this instance, the Examiner taking judicial notice appears to provide an element of the claims, which is not taught or suggested by any art of record. There is no art of record that suggests that cell activation levels are predictive of anything, and none that suggest methods that include measurement of cell activation levels, nor administering therapy to lowering such levels as a prelude to treatment or prophylactically. Further, there is no art of record that suggest that futhan lowers cell activation levels. The Examiner is taking judicial notice of allegations important to the rejection and combining them with references that do not suggest the claimed elements or methods.

In this instance, a reference or references supporting assertions by the Examiner should be provided. No references of record teach or suggest that tests for assessing cell activation are ever performed, that treatment options are evaluated based upon the level of cell activation nor that futhan or any compound or regimen could be used to lower cell activation prior to treatment for a disease or condition or as a way to improve treatment outcome or reduce risk of treatment nor as a prophylactic.

Rebuttal to the Examiner's specific statements

1) The Examiner states that "a doctor routinely checks his/her patients for blood pressure, temperature, etc." and questions why Applicant thinks "that a doctor would not check his patient for any type of disorder or disease." The Examiner asserts that claim 32 is allegedly so broad that it reads on any type of "cell activation" of any condition or disease and that there is nothing specific about claim 32. The Examiner asserts that "this is a normal thing for a doctor to do."

The claim does not recite checking a patient for any disease or disorder; but rather, it recites checking for cell activation. Cell activation is defined in the specification as "changes in and interactions among circulating white blood cells, including leukocytes, cells lining blood vessels, including endothelial cells, and platelets. These changes are evidenced by increased "stickiness" of cells,

changes in shapes of cells, free radical production and release of inflammatory mediators and enzymes. Activated cells project large pseudopods, and express adhesion molecules on their surfaces." (Specification at page 16, lines 18-24).

Further, cell activation, as defined in the specification, is a documented and normal physiological response of the immune system that is essential for survival. While cell activation was known to occur, it has never before been suggested as a diagnostic indicator or therapeutic target. At the time of filing, assessment of cell activation was not a known diagnostic procedure. It also has never before been suggested to treat elevated levels of cell activation by administering cell activation lowering therapy. Thus, it was not "a normal thing for a doctor to do."

Here it is shown that inappropriate or excessive levels of cell activation can be seen as a condition of the immune system that leads to or participates in or intensifies disease states. It is only by virtue of that which the Applicant has disclosed in the instant specification that one of ordinary skill in the art would be motivated to assess cell activation as a diagnostic indicator and use cell activation as an intervention point to prevent a disease or disorder, improve treatment outcome for a particular disease or disorder, or reduce the risk of a treatment for a particular disease or disorder.

Thus, with respect to the Examiner's questions of why Applicant thinks "that a doctor would not check his patient for any type of disorder or disease" and the Examiner's assertion that "there is nothing specific about claim 32," it is respectfully submitted that the claims do not recite a step of assessing "any disease or disorder." The claims recite a step of assessing **cell activation**, a specific and measurable condition of the immune system, that is not taught or suggested by any of the cited references.

2) The Examiner states that "if one were to follow applicant's logic, then a doctor would only check his patient's temperature if the patient showed any signs already of having temperature." The Examiner asserts that "one of

ordinary skill in the art also would check for "cell activation" to see if any levels of the patient had been elevated which is relative in and of itself."

As stated above, cell activation is a specific and measurable condition. None of the cited references, singly or in any combination, suggests assessing the level of cell activation. Use of cell activation levels as a diagnostic indicator and therapeutic target is presented in the instant specification for the first time. As discussed above, the level of cell activation is relevant in and of itself since inappropriate or excessive levels of cell activation have been found to be of significant importance generally, whether in good or poor health. It follows that assessment of cell activation levels and treatment of inappropriate levels is relevant whether a subject presents symptoms of a disease or not. It is only by virtue of that which Applicant has disclosed in the instant specification that one of ordinary of skill in the art would know this. The Examiner has not shown anything in the cited art or otherwise that would lead one of ordinary skill in the art to check cell activation levels and to then administer therapy to lower the cell activation levels. The cited art does not teach that it is desirable to check levels of cell activation, nor that lowering such levels prior to treatment of a disease or disorder or for prophylaxis is desirable.

Therefore, the Examiner has failed to set forth a *prima facie* case of obviousness.

* * *

In view of the above remarks and remarks of record, consideration and allowance of the application are respectfully requested.

Respectfully submitted,
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